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### Letters to the Editor

## Correspondence re: Gammon *et al.*, Environmental Toxins and Breast Cancer on Long Island. I. Polycyclic Aromatic Hydrocarbon DNA Adducts. 11, 677–685, 2002

### Letter

**Frederica Perera and Andrew Rundle**

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Gammon *et al.* recently reported results from the comprehensive Long Island Breast Cancer Case-Control Study<sup>1</sup> showing no consistent elevation in risk with increasing PAH-DNA adduct levels in white blood cells (CEBP, Vol. 11, 677–685, 2002). Their results are similar to our previous findings from a hospital-based, case-control study in New York City that did not find a consistent association between PAH/aromatic adducts in white blood cells and breast cancer (A. G. Rundle, A Molecular Epidemiologic Case Control Study of Breast Cancer, Doctoral Dissertation, 2000, Department of Epidemiology, Mailman School of Public Health, Columbia University, NY). In contrast to adducts in blood, however, in our study, elevated PAH-DNA adducts measured in breast tumor tissue from cases and normal tissue from controls were significantly associated with breast cancer (odds ratio 2.56, 96% confidence interval 1.05–6.24; Carcinogenesis, Vol. 21, pp. 1281–1289, 2000).

Our study included 100 cases and 105 controls enrolled before surgery and treatment from the same source population at Columbia Presbyterian Medical Center (now New York Presbyterian Hospital) in New York City. Thus, the controls were representative of the population from which the cases arose. Women who were diagnosed with benign breast cancer (excluding atypia) considered to be at relatively low risk of subsequent breast cancer comprised the control group. We did not see a correlation between adducts in blood and breast tissue, although adducts in tumor and nontumor breast tissue from the same cases were significantly correlated ( $P < 0.001$ ).

Unlike results on adducts and lung cancer (Tang *et al.*, Cancer Res. 2001, 61:6708–6712), it appears that the blood is not a good proxy for the target tissue in this instance, possibly because the breast represents a hormonal milieu. The results underscore the importance of obtaining both surrogate, target tissue, and suggest that PAHs are a risk factor for breast cancer. If confirmed, the results would open new avenues for prevention.

We thank Drs. Perera and Rundle for their interest in our recently published research on PAH<sup>1</sup>-DNA adducts assessed in peripheral blood in relation to breast cancer incidence among Long Island women (1). In their letter to the editor<sup>2</sup>, Drs. Perera and Rundle make three comments. First, they mention their research using PAH-DNA adducts in peripheral blood and claim that their findings are similar to ours. However, we are not aware that their peripheral blood results have been published, nor are they described sufficiently for us to comment on whether the two studies are similar.

Second, Drs. Perera and Rundle<sup>2</sup> describe the results of their already published research on DNA adduct levels as measured in breast tissue (2), work that we also cited and described in our recent publication (1). Drs. Perera and Rundle assert that their cases and controls arise from the same source population. The study included cases and controls selected from a single teaching hospital, which as described by Rothman and Greenland (3), is a design where “the source population is often not identifiable.” Moreover, merely coming from the same source population as the cases does not make a control group representative of that population, as Drs. Perera and Rundle imply.

Third, Drs. Perera and Rundle<sup>2</sup> suggest that PAH-DNA adducts as measured in breast tissue may be a better measure than adducts assessed from peripheral blood. They appear to base their assertion on comparing the odds ratio of 2.56 (95% confidence interval 1.05, 6.24) for detectable adducts in tumor tissue observed in their hospital-based study of ~200 subjects (2), *versus* the estimate of 1.35 (95% confidence interval 1.01, 1.81) for detectable adducts observed in peripheral blood in our population-based study of ~1000 subjects (1). They further suggest that PAH is a risk factor for breast cancer. We believe that these assertions are premature, because of the paucity of literature that has been published to date on this issue.

Currently, there are several interpretations that are consistent with the epidemiologic studies that have been reported to date that address the PAH-DNA adduct and breast cancer hypothesis (1, 2, 4). First, the odds ratio from the two studies (1, 2) cited in the paragraph above could be described as compatible (primarily attributable to the wide confidence interval estimates from the hospital-based study). This first interpretation would suggest that PAH-DNA adducts may be associated with breast cancer incidence, regardless of the method used to assess the body's exposure dose.

### Reply

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<sup>1</sup> The abbreviation used is: PAH, polycyclic aromatic hydrocarbon.

<sup>2</sup> F. Perera and A. Rundle. RE: Environmental toxins and breast cancer on Long Island. I. Polycyclic aromatic hydrocarbon DNA adducts. Cancer Epidemiol. Biomarkers Prev., submitted for publication, 2002.

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<sup>1</sup> The abbreviation used is: PAH, polycyclic aromatic hydrocarbon.

Alternatively, as recently described by several authors (5, 6), early reports of a strong link to human disease based on small numbers of subjects can be misleading; when replicated in larger studies, the estimates of effect often move closer towards the null. These authors are describing a common pattern in genetic association studies, yet it is also a pattern that is consistent with the few publications on the issue of PAH-DNA adducts and breast cancer, with smaller studies reporting higher estimates of effect (2, 4) and our large study reporting an estimate closer to the null (1). This alternative interpretation would suggest that these early reports may be false positives.

To resolve these issues, confirmation is needed using multiple assessment methods, larger sample sizes, and stronger study designs. Only through multiple repetitions and improved study methods can we determine whether PAH-DNA adducts are indeed a risk factor for breast cancer or just another false positive result.

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